to early cases and the facilities for providing group treatment. They could therefore most appropriately undertake this work and provide a national network of clinics for the prevention of chronic bronchitis. Clinics might also be established wherever there are groups of people exposed to special risks of respiratory disease, such as in certain industries.

However, a more active part in advising some patients individually and selecting others for further treatment is required of all who come into contact with those in the early stages of disease.

Summary

Chronic bronchitis is a major cause of sickness absence, misery, and death in this country. Chronic irritation by air pollution and cigarette smoke, and chronic or recurrent infection, contribute both to its development and to its progression.

An experimental group clinic designed to help patients with early symptoms has been run for two winters.

Difficulties in the recruitment of suitable patients are described. It is suggested that those attending mass *x*-ray units on account of a persistent cough or recent chest illness, and who have negative films, are a major source of potential bronchitics eminently suitable for preventive treatment.

The programme included instruction in breathing exercises, vaccination against influenza, the provision of antibiotics to be taken at the outset of a chest infection, the provision of a "smog" bottle, an attempt to stop patients smoking, and general health education.

A short-term follow-up of 109 patients indicates that the clinic is fulfilling a need and that many patients are following the advice given: 28% say they are setting time aside to do their breathing exercises, and a further 52% are doing them during their normal activities. Of those having chest infections, 80% followed the antibiotic regime suggested, though many failed to replenish their supply. Of 77 smokers, 28 (36%) stopped smoking, 24 (31%) decreased, 24 (31%) continued as before, and 1 (1%) increased.

The short time-interval between attendance and follow-up and the seasonal differences render changes in symptoms of doubtful significance, but cough and the production of phlegm decreased, particularly in those who stopped smoking.

It is suggested that other clinics on the lines of the one described should be started. Chest clinics are the most appropriate organizations to provide a service on a national scale, but an active part in selecting suitable patients must be played by all who come into contact with those in the early stages of disease.

We are grateful to Mr. Sohikish, of the Camden Rehabilitation Unit, who ran the physiotherapy session with enthusiasm throughout; to the late Dr. S. Leff, M.O.H. of Willesden; to Miss Parbery, S.R.N., of the Willesden Chest Clinic, who helped with the running of the clinic; and to our secretaries. We wish to thank Dr. H. Joules, of the Central Middlesex Hospital, Professor R. S. F. Schilling, of the London School of Hygiene and Tropical Medicine, and Dr. C. H. C. Toussaint, of the Willesden Chest Clinic, for the encouragement and help that they have given; and the North-West Metropolitan Regional Hospital Board, who made a research grant. We would also like to thank Pfizer and Co. for supplying flubron for use during the first winter and for the repeated loan of their film "Chronic Bronchitis," and the British Temperance Society, from whom the film "Time Pulls the Trigger" was repeatedly borrowed.

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UNUSUAL NEUROLOGICAL AND CARDIOVASCULAR COMPLICATIONS OF RESPIRATORY FAILURE

BY

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It is known that respiratory failure is often attended by neurological and cardiovascular complications. Most of the neurological complications—for example, drowsiness, depressed tendon reflexes, extensor plantar responses, and coma—are thought to result from hypercapnia with or without hypoxia. They have been well reviewed by Westlake, Simpson, and Kaye (1955) and by Sieker and Hickam (1956).

Similarly, the majority of cardiovascular complications, such as acute congestive cardiac failure and atrial fibrillation, are well known and have been described and discussed by many authors—for example, Harvey and Ferrer (1960).

This paper deals mainly with additional neurological and cardiovascular complications which are not so well documented, but which we have observed in a number of patients.

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The Series.—We have made a prospective study of all patients admitted in respiratory failure, with or without cor pulmonale, to the Central Middlesex Hospital during the winter of 1961–2. Many of them had previously been seen at the hospital or at the Willesden Chest Clinic. Neurosurgical complications or cardiovascular complications, or both, were observed in 17 patients.

Methods

On admission a history of previous respiratory illness and disability and of the present episode was taken. In the examination particular attention was paid to the clinical assessment of hypoxia and hypercapnia, and to the respiratory and cardiovascular systems. Investigations always included a chest *x*-ray examination and an initial estimation of the mixed venous P_{CO_2} using the rebreathing method of Campbell and Howell (1960). The latter investigation was repeated within the first hour of treatment and then

again as often as necessary (at least once a day during the acute period). Sometimes an electrocardiogram was taken.

In the management oxygen was given continuously by Venturi mask (Campbell, 1960) usually starting with 25–29% oxygen. Occasionally oxygen was given by nasal catheter at 2 litres/minute. Respiratory stimulants were given only when the mixed venous P_{CO_2} rose within an hour or less of starting continuous oxygen, or if the patient was in coma on admission. In fact, respiratory stimulants were nearly always required. Nikethamide (250 mg./ml. in doses of up to 2 ml. half-hourly) was usually given, either by slow intravenous injection through a Gordh's needle or by intramuscular injection. Occasionally ethamivan ("vandid") or amiphenazole ("daptazole") was used. Treatment also always included bronchodilators (especially aminophylline, 0.25–0.5 g. by intravenous injection up to three times daily), antibiotics, physiotherapy, and sometimes steroids, digoxin, and diuretics. Tracheostomy was performed on four patients in whom medical treatment alone was thought to be inadequate. Mechanical respirators were not used.

Progress and developments were recorded on a chart such as is shown in Fig. 1. Post-mortem examination was performed on all patients who died.

Results

All patients had the history and physical signs of an acute exacerbation of chronic non-specific respiratory disease. All were cyanosed, had physical signs of hypercapnia, and had mixed venous P_{CO_2} levels above the upper limit of normal (50 mm. Hg).

Neurological Complications

Neurological manifestations of hypercapnia with hypoxia—for example, drowsiness, confusion, depressed tendon reflexes, extensor plantar responses, headache, and coma—were often seen. These were always transient: they disappeared when hypercapnia and hypoxia were relieved. They are considered in greater detail in another paper (Gross and Hamilton, 1963).

In addition, however, five patients developed major and fatal neurological complications. These were not due to hypercapnia in that they were not transient and occurred when the mixed venous P_{CO_2} had been considerably reduced and signs of hypercapnia were minimal or absent. Evidence is given that they may have been due to cerebral hypoxia.

All five patients were in severe respiratory failure on admission and subsequently died.

Case 1.—A woman of 61 collapsed five minutes after removing her Venturi mask on the second day of admission. Tracheostomy and recommencement of oxygenation produced some initial benefit, but she subsequently had several epileptic convulsions (not related to the administration of nikethamide) and died on the fourth day. Post-mortem examination showed generalized cerebral oedema with very little atheroma of the cerebral blood-vessels.

Case 2.—In this case, that of a man aged 62, dementia (with full consciousness) appeared for the first time on the third day and progressed to coma and death on the fifth day. Post-mortem examination showed generalized cerebral oedema with very little atheroma of the cerebral blood-vessels.

Case 3.—A man of 52 was found unrousable on the seventh morning, 36 hours after oxygen was stopped; left hemiplegia progressed to decerebrate rigidity. He improved considerably and regained consciousness when oxygen was recommenced, but subsequently gradually deteriorated, dying on the seventeenth day. Post-mortem examination showed generalized cerebral oedema and softening, most marked in the cerebellum; there was very little atheroma of the cerebral blood-vessels.

Case 4.—A man of 52 had left hemiplegia and coma on the fifth day, 36 hours after stopping oxygen. He improved at first with restarting of oxygenation, but subsequently deteriorated and died on the sixth day. Post-mortem examination showed generalized cerebral oedema and no atheroma of the cerebral blood-vessels.

Case 5.—A woman of 72 had quadriplegia and coma on the fifth day, 24 hours after oxygen was stopped. Initially there was slight improvement with recommencement of oxygenation, but subsequently she deteriorated, dying on the seventh day. Post-mortem examination showed generalized cerebral oedema with moderate atheroma of the cerebral blood-vessels. A chart of this patient's progress is shown (Fig. 1).

Discussion of Neurological Complications

Three factors appear to be associated with the occurrence of the neurological complications described above.

1. *Acute Exacerbation.*—The average duration of the acute exacerbation before admission to hospital was 23.0 days for these patients as compared with an average of 11.7 days for nine similar patients who did not suffer complications.

2. *Cessation of Oxygenation.*—In four patients (cases 1, 3, 4, and 5) the complication occurred between 5 minutes and 36 hours of stopping continuous oxygenation. The initial improvement in their condition and their subsequent deterioration are reminiscent of cases of anoxic cerebral damage resulting from anaesthetic accidents reported by Argent and Cope (1956).

3. *Rapid Fall of Mixed Venous* P_{CO_2}.—In all five patients the mixed venous P_{CO_2} had been reduced considerably by means of respiratory stimulants—more rapidly in these patients than in others. During the 48 hours before the complication occurred it had fallen by an average of 27 mm. Hg. In nine other patients without complications

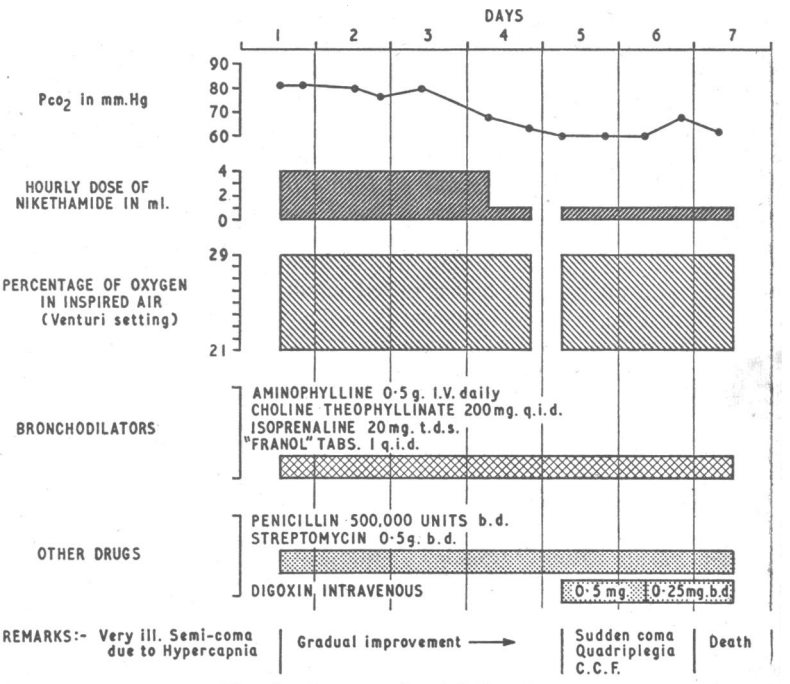

FIG. 1.—Progress chart of Case 5.

who were matched for the initial height of the mixed venous P_{CO_2}, the P_{CO_2} fell by a maximum of 18 mm. Hg over the same length of time (second and third days).

There is physiological evidence that a fall in the P_{CO_2} is followed by a fall in the cerebral oxygen supply. Kety and Schmidt (1948) have shown that experimental hypercapnia and hypoxia cause cerebral vasodilatation in normal men. The more powerful element, however was hypercapnia. Furthermore, Patterson, Heyman, and Duke (1952) found that the administration of oxygen to patients in respiratory failure (thus relieving hypoxia but increasing hypercapnia) was followed by an overall increase in the cerebral blood flow. Conversely, Schmidt and Pierson (1934) have shown that in the dog a lowering of arterial P_{CO_2} reduced cerebral blood flow much more than did relief of hypoxia. Lambertsen, Semple, Smyth, and Gelfand (1961) also consider that cerebral blood flow depends mainly on arterial P_{CO_2}. (Systemic blood-pressure appears to be relatively unimportant.)

Thus the result of a fall in P_{CO_2} is a fall in cerebral blood flow. In addition to this, a fall in the P_{CO_2} shifts the oxygen dissociation curve to the left, and this change hinders the removal of oxygen from the blood in the tissues, thus further reducing cerebral oxygen supply.

The deliberate lowering of the P_{CO_2} by respiratory stimulants may therefore abolish a "protective" effect of hypercapnia on cerebral oxygen supply in respiratory failure. If, in this situation, oxygenation is discontinued there is an even greater danger of anoxic cerebral damage than if the P_{CO_2} had been allowed to remain at a higher level. It seems likely that in our patients the coincidence of a rapidly falling P_{CO_2} and the cessation of oxygenation may have been sufficient to produce irreversible anoxic cerebral damage.

At the beginning of the winter we concentrated on the relief of both hypoxia and hypercapnia. It was during this period that the neurological complications described above occurred. Later we adopted a policy of treating hypoxia without deliberately lowering the P_{CO_2}. No major neurological complications occurred in the patients in whom we did this. If the mixed venous P_{CO_2} tended to rise we were always able to prevent it from reaching levels where hypercapnia of itself would be dangerous.

Cardiovascular Complications

Most of the cardiovascular complications in our series are well recognized: acute congestive cardiac failure occurred for the first time in seven patients; a recent increase in heart size, without signs of congestive cardiac failure, occurred in two; atrial fibrillation was found in four; and all patients had a raised jugular venous pressure, but not necessarily oedema, during the severe phase of respiratory failure. All these complications responded to treatment.

There were three patients, however, in whom sudden or progressive cardiovascular deterioration, resulting in death, occurred quite unexpectedly and failed to respond to treatment. In no case was a satisfactory cause for the deterioration diagnosed before death. Post-mortem examination revealed pulmonary-artery thrombosis in each case. The details of these patients are as follows.

Case 6

A man of 64 had a 40-year history of chronic non-specific respiratory disease and a 10-year history of cor pulmonale. There was no history to suggest previous venous thrombosis or pulmonary embolism.

On admission he was in an acute exacerbation of his respiratory disease with very severe congestive cardiac failure. The blood-pressure was 100/70 mm. Hg. There was a marked sternal lift. The second sound in the pulmonary area did not appear to be accentuated, but it was difficult to hear on account of the volume of other noises in the chest. No murmurs were heard. The electrocardiogram showed severe right ventricular hypertrophy. The chest *x*-ray film showed a cardiothoracic ratio of 53% with a large pulmonary artery but decreased vascular markings in the lung fields.

He improved over the course of the next two weeks but then suddenly deteriorated. He complained of epigastric pain and was found to be in rapid atrial fibrillation. There was a sudden increase in the signs of congestive cardiac failure. The blood-pressure was 90/? mm. Hg and the mixed venous P_{CO_2} had risen from 72 mm. Hg on admission to 80. There were no signs of deep-vein thrombosis. A tentative diagnosis of myocardial infarction or pulmonary embolism was made and he was treated accordingly. Continuous oxygenation was restarted and he was given anticoagulants. He failed to improve, however, and died 36 hours later.

Post-mortem examination showed: "Acute upon chronic bronchitis and emphysema. Gross right ventricular hypertrophy and dilatation. The pulmonary artery was almost completely occluded at its bifurcation by an old adherent thrombus, which extended approximately 5 cm. into each main branch. The centre of the mass of thrombus was necrotic." There was also "severe atheroma of the smaller branches of the pulmonary arterial tree." No evidence was found of peripheral venous thrombosis or that the thrombus had formed around a recent or old embolus. A photograph of the specimen is shown (Fig. 2).

Case 7

A man of 67 had had chronic non-specific respiratory disease for about 20 years and ankle oedema for one year. Hypothyroidism had been diagnosed on clinical grounds two weeks before admission and he was on L-thyroxine. There was no history suggestive of deep-vein thrombosis or of pulmonary embolism in the past.

On admission he was in mild respiratory failure and severe congestive cardiac failure. The blood-pressure was 150/100 mm. Hg. The cardiac impulse was diffuse and tapping, and there was a triple rhythm over the lower end of the sternum. The second sound in the pulmonary area was thought to be

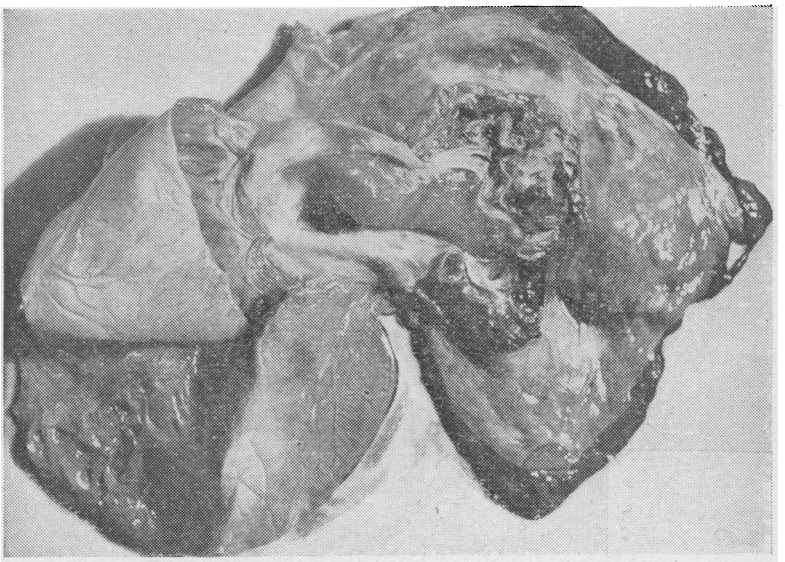

FIG. 2.—Case 6. Photograph of heart and pulmonary artery opened, showing a large old thrombus extending from the main pulmonary artery into the right and left branches.

normal. It was also thought possible that he had mild hypothyroidism.

The electrocardiogram showed right ventricular hypertrophy and generalized myocardial damage. On chest *x*-ray examination the cardiothoracic ratio was 56% and there was enlargement of the pulmonary artery. The lung fields showed nothing of note. The mixed venous P_{CO_2} was 74 mm. Hg.

He was given continuous oxygenation and the usual treatment for cor pulmonale and respiratory failure; L-thyroxine was continued. However, he failed to make any progress apart from a fall in the mixed venous P_{CO_2} to 48 mm. Hg. He lapsed into coma on the sixth day and died the next day.

Post-mortem examination showed chronic bronchitis and emphysema, moderate right and left ventricular hypertrophy, and right ventricular dilatation. The right pulmonary artery was approximately half occluded by old laminated thrombus adherent to the wall and extending into its branches. There was also thrombus adherent to atheromatous plaques in the thoracic aorta, and the coronary arteries were severely occluded. There was no evidence of peripheral venous thrombosis.

Case 8

A man of 59 had had chronic non-specific respiratory disease for approximately 10 years and cor pulmonale for at least 18 months. There was no past history suggestive of deep-vein thrombosis or pulmonary embolism.

On admission he was in mild respiratory failure and very severe congestive cardiac failure. There were signs of consolidation of the upper lobe of the right lung. The blood-pressure was 140/90 mm. Hg. There was a marked sternal lift with accentuation of the second sound in the pulmonary area.

The electrocardiogram revealed gross right ventricular hypertrophy. Chest *x*-ray examination showed a cardiothoracic ratio of 58% and enlargement of the pulmonary artery. In addition there was cavitation of the right upper lobe which had not been present two months previously. *Haemophilus influenzae* (but not tubercle bacilli or *Staphylococcus aureus*) was cultured from the sputum. His mixed venous P_{CO_2} was 77 mm. Hg as compared with 67 mm. Hg when in relative health one year previously.

He was given full treatment for cor pulmonale, respiratory failure, and pneumonia, and made excellent progress during the next three weeks. At the end of this period, however, he suddenly deteriorated. He became cold and clammy, and the pulse was rapid and small. The blood-pressure had fallen to 100/50 mm. Hg. Otherwise no change was observed in the physical signs, no signs of deep-vein thrombosis, and no chest pain.

He died within an hour, a tentative diagnosis of myocardial infarction or pulmonary embolism having been made.

Post-mortem examination showed chronic bronchitis and emphysema and multiple non-tuberculous cavities in the right upper lobe, and right ventricular hypertrophy. The right pulmonary artery was completely occluded by an old adherent laminated thrombus. There was no evidence of peripheral venous thrombosis.

Discussion of Pulmonary Artery Thrombosis

Pulmonary-artery thrombosis is a recognized complication of pulmonary disease and has been reported in chronic pulmonary tuberculosis and carcinoma of the bronchus (Savacool and Charr, 1941; Magidson and Jacobson, 1955; Platts, Hammond, and Stuart-Harris, 1960). In cor pulmonale due to chronic non-specific respiratory disease Fulton (1953) and Flint (1954) found no case of pulmonary-artery disease in necropsies on 24 and 58 cases respectively. But Wheeler, Croke, and Berthrong (1962) reported it in 4 out of 44 necropsies on patients with severe emphysema.

Ball, Goodwin, and Harrison (1956) cite pulmonary hypertension and atheroma as aetiological factors. In a large percentage of their cases pulmonary-artery thrombosis was secondary to pulmonary embolism. This was also the experience of Goodwin, Harrison, and Wilcken (1963), who reported 19 cases of obliterative pulmonary hypertension, of which at least six were associated with thrombosis in the main pulmonary artery or its major branches. Four of these six patients had a history suggestive of pulmonary embolism; the remaining two had a history of chronic respiratory disease to which the pulmonary-artery thrombosis may have been secondary.

There was no history of pulmonary embolism in our patients, and respiratory disease preceded congestive cardiac failure by many years in every case. It therefore seems likely that thrombosis occurred *in situ* as the sequel to pulmonary hypertension. Atheroma of the pulmonary arterial tree was present in two cases. Possibly the cavitation of the right upper lobe in Case 8 was the result of infarction in the manner described by Ehrner, Garlind, and Linderholm (1959).

It was the clinical picture which was most striking in our cases. All presented with an unremarkable acute exacerbation of respiratory failure and cor pulmonale. In one case the congestive cardiac failure did not respond to treatment. In two cases the patient initially improved, and then quite suddenly and unexpectedly deteriorated with severe congestive cardiac failure. Diagnoses of acute myocardial infarction or pulmonary embolism were made; yet at necropsy the thrombi had evidently been present for some time. Indeed, the obstruction in the pulmonary artery in Cases 6 and 7 was so great that it was remarkable that the patients survived as long as they did.

Summary

A prospective study has been made of all cases of respiratory failure admitted to the Central Middlesex Hospital during the winter of 1961–2.

In addition to the well-known neurological and cardiovascular complications that occur in respiratory failure two other complications are reported and discussed. The first is anoxic cerebral damage. It is suggested that this may be precipitated by the coincidence of a rapid fall in the P_{CO_2}, which may reduce cerebral oxygen supply, and the cessation of continuous oxygenation. The second is pulmonary-artery thrombosis, which was found at post-mortem examination of three patients with respiratory failure and cor pulmonale who died unexpectedly.

The survey of which this paper and the next (Gross and Hamilton, 1963) are the result was made possible by the great assistance and co-operation of the sisters, nursing staff, and medical secretaries of the hospital. We acknowledge with gratitude the interest and encouragement of Dr. H. Joules, Dr. C. H. C. Toussaint, Dr. K. P. Ball, and Dr. R. Asher, under whose care all the patients were. We also wish to thank Dr. R. A. B. Drury and Dr. A. Pomerance for permission to report their post-mortem findings, and for their assistance with the pathological material. In particular we wish to thank Dr. Moran Campbell, who gave us a great deal of assistance with the preparation of this paper. Miss D. M. Barber kindly executed the diagrams in this and our other paper, and Mr. A. Booker took the photograph.

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CORRELATION BETWEEN THE PHYSICAL SIGNS OF HYPERCAPNIA AND THE MIXED VENOUS P_{CO_2}

BY

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Many patients with chronic non-specific respiratory disease have persistently raised P_{CO_2} levels, without the physical signs of hypercapnia, during periods of relatively good health. In an acute exacerbation the P_{CO_2} may rise still further and the physical signs of hypercapnia may appear. Therefore the significance of a raised P_{CO_2} in an acute exacerbation is in doubt unless the patient's usual P_{CO_2} level is known or unless the hydrogen-ion concentration is estimated.

It would be valuable to be able to assess on clinical grounds the amount by which the P_{CO_2} has been elevated during the course of an acute exacerbation. We have therefore sought a correlation between the physical signs of hypercapnia and the P_{CO_2} estimations of patients admitted to hospital in acute respiratory failure. We have also tried to correlate these signs with the rise in P_{CO_2} above each patient's usual level.

The Series.—A prospective study was made of all patients admitted in respiratory failure to the Central Middlesex Hospital during the winter of 1961–2. Many had previously been seen as out-patients either at that hospital or at the Willesden Chest Clinic.

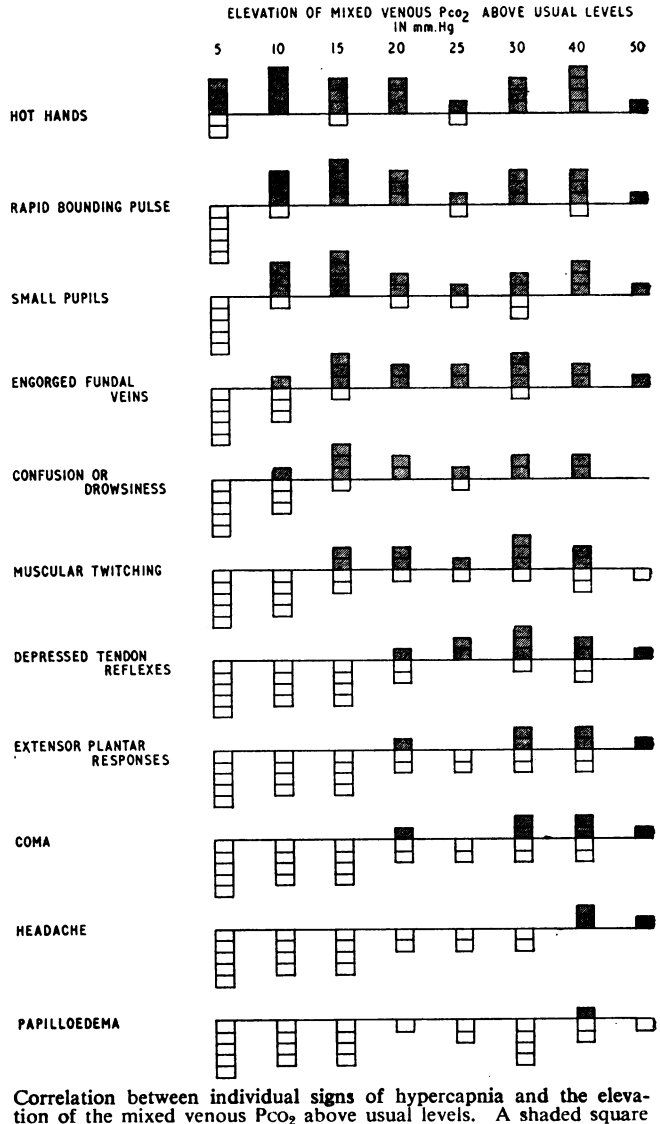
Methods

On admission to hospital of the patients we recorded the presence or absence of each of the physical signs which have been ascribed to CO_2 retention. These are peripheral vasodilatation; a rapid bounding pulse; tremor or twitching, most marked in the forearms; confusion or drowsiness; depressed tendon reflexes; extensor plantar responses; small pupils; engorged fundal veins; papill-oedema; and coma. Headache, although not a physical sign, was also recorded and is discussed as one for convenience. That these signs were not due to hypoxia was shown by the failure of oxygen administration to abolish them.

After the physical examination the mixed venous P_{CO_2} was estimated by the rebreathing method of Campbell and Howell (1960).

Finally, wherever possible we recorded the mixed venous P_{CO_2} during relative health, or the "usual mixed venous P_{CO_2}," as we shall call it. In some cases this was known from previous estimations; in others it was estimated when the patient had fully recovered. Unless it was possible to estimate the usual mixed venous P_{CO_2} level in one of these ways the patient was excluded from the results. Thus no patient in whom the usual mixed venous P_{CO_2} had not been previously estimated and who subsequently died or did not regain his previous state of health is included in this report.

We were able to collect this information for 26 episodes in 23 patients.



Correlation between individual signs of hypercapnia and the elevation of the mixed venous P_{CO_2} above usual levels. A shaded square above the line for each sign indicates its presence in one case; an unshaded square below the line indicates its absence in one case.

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